A STUDY OF MALIGNANT CERVICAL LYMPHADENOPATHY WITH UNKNOWN PRIMARY.

Dissertation submitted in partial fulfillment of the regulations required for the award of

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Branch I

The TamilNadu
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CERTIFICATE

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DECLARATION

I solemnly declare that the dissertation titled **"A STUDY OF MALIGNANT CERVICAL LYMPHADENOPATHY WITH UNKNOWN PRIMARY"** was done by me at Coimbatore Medical College and Hospital, Coimbatore during the period of August 2003 to December 2005 under the guidance and supervision of **Prof.Dr.A.RAMAMOORTHY M.S.**

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CONTENTS

INTRODUCTION

Head and neck cancers account for 2.8% of all newly discovered cancers[1]. Metastatic carcinoma within cervical lymph nodes with an unknown primary tumour site accounts for 3% to 5% of all head and neck cancers.[1]

The control of such regional metastatic disease constitutes a significant part of the process of treating head and neck cancer. The presence of an enlarged node proven histologically positive for metastasis is an ominous findings and as a general rule decreases the 5-year survival rate by at least 50%.When nodal involvement becomes multiple extends low in neck, no patient gets cured regardless of the treatment given[2].When the primary site of carcinoma is known, focused therapy to the primary site and cervical lymphadenopathy can be given. Without this knowledge clinicians are obligated to treat the entire pharyngeal axis and larynx to cover the possible origins of the metastatic carcinoma. The occult primary treatment regimen results in a significant increase in morbidity to the patient. Proper understanding of the anatomy and detection of cervical metastatic disease is crucial to this process.

AIMS OF THE STUDY

1. To find age and sex incidence of the malignant cervical lymphadenopathy with an unknown primary.
2. To analyse the histopathological types common in our population.
3. To stage the disease at the time of presentation
4. To interpret the possible site of primary based on the nodal involvement.
5. To describe the various investigations used to identify the primary site.
6. To discuss the ideal treatment modality for the patients.

REVIEW OF LITERATURE

ANATOMY OF THE CERVICAL LYMPHATICS

The lymphatics has three components ; the capillaries, vessels and the nodes.

Capillaries

Larger than ateriovenous capillaries, the lymphatic capillaries are thin walled, with a single layer of endothelial cells. Lymphatic capillaries are found in all tissues; however they are more abundant in the upper respiratory and gastrointestinal tracts. Pooled capillaries drain lymphatic fluid into lymphatic vessels.

Vessels

As in the capillaries the vessels have a single layer of endothelial cells surrounded by an inner longitudinal elastic layer. This first muscle layer is surrounded by a circular smooth muscle layer, which in turn is enveloped by an outer connective tissue layer. Lymphatic vessels contain many more valves than the venous system, with the lymph circulation entirely dependant on compression by surrounding muscles, lymphatic vessels drain into lymph nodes.

Nodes

These nodes are of variable size. Typically as many as 75 nodes are located on each side of the neck. Nodes contain a subcapsular sinus below a prominent capsule, into which lymphatic fluid drains. This capsule is often the first site of metastatic growth. The fluid permeates the substance of the node (composed of cortex and medulla) and exists through the hilum to enter more lymphatic vessels. These nodes are located between the superficial cervical and prevertebral fascia and thus are very amenable to surgical removal. The lymphatic fluid eventually enters the venous system at the junction of the internal jugular and subclavian veins[3].

Except for a few retrovisceral nodes and those deep to the sternomastoid muscle all become palpable when enlarged. Because tumours have no primary lymphatics, cancer cells presumably gain access to the lymphatic system at the periphery through clefts between lymphatic endothelial cells.

Lymphatic vessels are continuously contracting; actin like filaments are observed in lymphatic endothelial cells. The afferent lymphatics join a marginal sinus in the cortex of individual lymph nodes. When cancer cells lodge in lymph nodes, proliferation first occurs in the periphery and later in the medulla. From there anastamosing channels penetrate the body of the node to form hilar efferent channels into which

the marginal sinuses drain directly. The efferent channels from a group of nodes form lymphatic trunks that in turn form collecting trunks. The collecting trunks drain into the venous system. According to traditional view, cancer cells in the lymphatic system can gain access to the blood stream only through these terminal collecting trunks at their junctions with major blood vessels.

LYMPHATICOVENOUS COMMUNICATIONS

Many lymphaticovenous communications exist normally in the body. Embryonically lymphatics originate from buds of venous endothelium. Substances of varying sizes have been demonstrated to pass from lymphatics to veins within lymph nodes.

Cells that enter lymphatics are transported to lymph nodes in the afferent vessels, are deposited in the peripheral subcapsular sinuses of the node, but subsequent process are variable, based on the existence of lymphatcovenous anastamosis.

Cancer cells may permanently lodge in the lymph nodes, may traverse nodes taking egress by efferent lymphatics or through lymphaticovenous communications within nodes to become hematogenously disseminated or may completely bypass lymph nodes to enter the blood vascular system[4].

Primary hematogenous spread may occur when cells gain access to small blood vessels in the tumour stroma; such vessels develop from

existing host vessels, presumably as a response to tumour angiogenesis. Blood borne tumour cells may also traverse interstitial spaces, invade the lymphatics and then disseminate via lymphatics.

Thus in addition to the classical route from the afferent channels through the medulla to the efferent channels, cells may bypass the medulla by means of the marginal sinus or may enter the blood stream in the node. Additionally lymph nodes may be completely bypassed through collateral channels, although this route is enhanced by local obstruction to lymphatic flow caused by metastases or reactive lymph node hyperplasia, including sinus histiocytosis. Tumuor cells can bypass the nearest regional nodes and proceed to more remote lymph nodes. This phenomenon of skip metastases is seen not infrequently in head and neck cancer patients. There is apparently no orderly progression down lymphatic chains and hence into the blood vascular system when lymphatic depots are saturated[5].

The many oppurtunities for lymphaticovenous and interlymphatic communication prevent any rigid discrimination between hematogenous and lymphogenous metastasis anatomically. This two way communication may well account for confused patterns of metastasis involving the two circulatory systems and argues against metastasis being confined to one or the other except perhaps in early subclinical cancer.

Although such lymphaticovenous communications exist, whether or not they are quantitatively significant under normal physiologic conditions is unknown. It is generally thought that these channels are probably dormant until called in for action by imbalance in intravascular pressure precipitated by mechanical obstruction.

Reversal of lymph flow can be easily produced; retrograde flow of lymph is enhanced and filtering efficiency of lymph nodes is decreased by inflammation, fibrosis from radiation and tumour growth with in them. Tumour emboli are able to disseminate through existing or opened anastamoses or in newly formed collateral channels.

WHY CARCINOMA FAVOUR LYMPHATIC SPREAD

An early step in the metastatic process is the detachment of cancer cells or cluster of cells from their parent tumours .Clusters have better chance of survival than single cells.

Single cancer cells tend to enter the blood or lymphatic systems equally, whereas cell clumps are more restricted to entering the blood vessels than the smaller lymphatic channels.

Because of intimacy with their own blood supply, sarcomas have a better chance than carcinomas of gaining early access to blood channels and with their comparatively lower thrombogenic activity they have less chance of being held up by intravascular thrombosis than carcinoma cells.

Sarcomas also preferentially separate as multicelluar units rather than as single cells. This would promote their survival in the blood stream and would tend to hinder their access to lymphatic systems.

Conversely, the greater tendency of carcinomas to release single cells would favour early direct lymphatic spread.

ANATOMY OF NECK NODES

The nodal system of the head and neck consists of two groups ,a terminal collecting group known as the deep cervical chain and an outlying intermediary group arranged into two circles,the ‘outer circle’ and the ‘inner circle’.the internal jugular vein which remains surrounded by nodes of the terminal group lies vertically between the outer and inner circles of the outlying group.[6]

All the lymph from the head and neck ultimately reaches the nodes of the terminal group either directly from adjacent tissues or indirectly from nodes of the outlying group. In turn lymph from the terminal group drains into the jugular lymph trunk that joins the thoracic duct on the left, but on the right side opens directly into the jugular or the branchiocephalic vein.

Superior deep cervical group

This group of nodes drain the soft palate, tonsil, posterior oral tongue, base of tongue, pyriform sinus, supraglottic larynx. The important node of this group is jugulodigastric node otherwise known as tonsillar

node. It lies just below and behind the angle of mandible. It is enlarged in all cases of tonsillar pathology.

Middle deep cervical group

This group drains the supraglottic larynx, lower pyriform sinus and post cricoid area.

Inferior deep cervical group

This drains the thyroid, trachea and cervical oesophagus. The important node of this group is juguloomohyoid. This lies in the intermediate tendon of omohyoid and receives lymph from tongue and submental node.

Spinal accessory chain

Lies along the course of the spinal accessory nerve and receives lymph drainage from scalp, nape of neck and from upper retropharngeal nodes.

Left scalene node

This is located at the junction of subclavian with the thoracic duct and receives drainage from thoracic duct. It is an important node to be looked for in cases of infraclavicular primaries.

Supraclavicular nodes

This receives afferents from spinal accessory chain and they are located in the posterior triangle of neck and occasionally may be involved in case of infraclavicular primaries.

SUPERFICIAL GROUP OF NODES

This is further divided into

a. inner circle of outlying group and

b. outer circle of outlying group of nodes

Outer circle of outlying group

This forms a collar in the cervical region.

Occipital nodes

This lies in the apex of posterior triangle and receives drainage from scalp and sends efferents to deep cervical group.

Post auricular group

Lies superficially over the mastoid attachment of sternomastoid and receives afferents from post auricular area, scalp and drain into upper deep cervical group.

Pre auricular nodes

This lies in front of the tragus and receives drainage from scalp, forhead, pinna, temple, eyelid and external auditory meatus and ultimately drains into deep cervical group.

Parotid and facial nodes

Lies within the substance of parotid gland and drains the orbit , parotid and infratemporal fossa. It sends in efferents to deep cervical group.

Buccal nodes

Lies over the buccinator muscle near lower border of mandible. Drains cheek, lower eyelid, sends efferents to jugulodigastric node.

Submental nodes

This is a group of nodes numbering 3-4, lies in the submental triangle and over mylohyoid muscle. Receives afferents from median plane structures and drains the chin and portion of lower lip, mid portion of gingival, floor of mouth, tip of tongue and nasal vestibule. It sends efferents to submandibular group.

Submandibular nodes

Lies in the submandibular triangle over the submandibulr gland itself. Facial artery is in close relation with this node. This group drains the centre of forehead, nose, upper lip, floor of mouth, cheek, gums, major part of tongue and paranasal sinuses(frontal, ethmoidal, maxillary).It ultimately drains into jugulo digastric and jugulo omohyoid nodes.

INNER GROUP OF OUTLYING NODES

This nodes lie in relation to upper aerodigestive tract and drains larynx, trachea and pharynx. All nodes ultimately drain into deep cervical group.

Infra hyoid nodes

Lies in relation to throhyoid membrane and drains the hypopharynx.

Prelaryngeal nodes

It is situated in the conus elasticus of the larynx and drains the larynx and superior part of isthmus of thyroid.

Pretracheal nodes

Situated anteriorly and in close relation with inferior thyroid veins and drains trachea and inferior part of isthmus of thyroid.

Paratracheal nodes

Flanks trachea and oesophagus on either side of the course of recurrent laryngeal nerve and drains trachea and cervical oesophagus.

Retropharyngeal nodes

Consists of one median and two lateral groups. Receives drainage from nasopharynx, auditory tube and adjacent vertebra.

CLASSIFICATION OF CERVICAL NODE GROUPS

Spread patterns of cancer from various primary sites in the head and neck to the cervical nodes have been documented in retrospective analyses of large group of patients undergoing neck dissections. Since the first descriptions of nodal groups, various classification systems have been described.

To address surgical management of early stage neck metastasis via neck dissection, various authours have proposed a number classification schemes. This lack of uniformity and standardization results in redundancy, misinterpretation and confusion among clinicians. The most widely accepted terminology was originally described by a group of head and neck surgeons at Memorial Sloan-Kettering Hospital. This classification uses neck levels and divides each side of the neck into 7 separate regions[7]

- **Level I** is bordered by the body of the mandible, anterior belly of the contralateral digastric muscle and anterior and posterior bellies of the ipsilateral digastric muscle. Two nodal subgroups are found, the submental group (Ia) is found in the submental triangle(anterior belly of digastric muscle and the hyoid bone),and the submandibular group (Ib) is found within the submandibular triangle (anterior and posterior bellies of the digastric muscle and the body of the mandible)

- **Level II** nodes are located around the upper third of the internal jugular vein, extending from the level of the carotid bifurcation inferiorly to the skull base superiorly. The lateral boundary is formed by the posterior border of the strenocleidomastoid muscle. Medial boundary formed by the stylohyoid muscle. Two subzones are described; nodes located anterior to the spinal accessory nerve are part of level IIa and those nodes posterior to the nerve are located in level IIb.
- **Level III** group defines the middle jugular group nodes limited by carotid bifurcation superiorly and the cricothyroid membrane inferiorly. The lateral border is formed by the posterior border of sternocleidomastoid muscle. The medial margin is formed by the lateral border of the sternothyroid muscle.
- **Level IV** contains the lower jugular group and extends from the omohyoid superiorly to the clavicle inferiorly. The lateral border is formed by the posterior border of sternocleidomastoid muscle. The medial border is formed by the lateral border of the sternothyroid.
- **Level V** nodes re found in the posterior neck triangle, bordered anteriorly by the posterior border of the sternocleidomastoid muscle. Posteriorly by the anterior border of the trapezius and inferiorly by the clavicle. Level V includes the spinal accessory, transverse cervical and supraclavicular groups.

- **Level VI** nodes are located in the anterior compartment. These nodes surround the middle visceral structures of the neck from the level of the hyoid superiorly to the suprasternal notch inferiorly.
- **Level VII** nodes are the paratracheal nodes inferior to the suprasternal notch in the upper mediastinum.

PREDICTABLE ROUTES OF NODAL METASTASIS FROM PRIMARIES

Cancers of the oral cavity have a predictable manner of spread to the cervical nodes. Depending on the site of primary certain patterns of metastatic involvement are evident.

Lesions of lip, anterior buccal mucosa, anterior gingival and floor of mouth are typically metastatic to submandibular and submental group of nodes. Lesions of tongue, posterior gingival and retromolar area involves upper deep cervical chain commonly. The submandibular node is the commonest node to be involved in carcinomas of floor of mouth and jugulodigastric is the commonest node involved in cancers of oral tongue.

The oropharynx consisting of retromolar trigone, anterior fauces, tonsil, soft plate and base of tongue drains primarily into juguodigastric node. The commonest node to be involved in tonsillar carcinoma was jugulodigastric node. Cancers of soft palate, base of tongue and oropharyngeal wall, because of proximity to midline tended to involve

bilateral jugulodigastric and rarely bilateral posterior triangle nodes (Lindberg et al).

Tumours of the nasopharnx most commonly metastasise to jugulodigastric nodes, bilaterally and in significant number of patients posterior triangle is also involved.

Tumours of the hypopharynx and supraglottic larynx tended to metastasise to jugulodigastric nodes followed by mid and lower deep cervical chains.

Tumours of thyroid commonly involved upper or lower deep cervical group of nodes depending on site of tumour (upper pole or lower pole).

SEQUENTIAL SPREAD

Not only is the topograghic location of involved nodes predictable for the various anatomic sites, but the sequential spread from one echelon to the other is also predictable. If the first echelon of lymphatics is not involved, the probability of involvement of the next echelon is low. In lateralized lesions the probability of contralateral metastasis is low when the ipsilateral side of the neck is clinically negative. The probability increases as the extent of ipsilateral metastases increases. In 1997 Molinari and colleagues used a statistical approach to predict the primary site based on the number and location of cervical node metastasis. This

type of information is very useful in patients who present with an unknown primary[8].

MECHANISM OF LYMPH NODE METASTASIS

The current hypothesis on the development of malignancies relate to alterations in the normal mechanisms of cellular proliferation and differentiation and a failure of cell death(apoptosis).This loss of growth control of genetic mutations, including the activation of proto-oncogenes and/or inactivation of tumour suppressor genes. The resulting phenotypic changes provide cancer cells a growth advantage, including loss of response to normal growth controls, defects in response signals for programmed cell death, resistance to cytotoxicity, and defects in terminal differentiation.

Proposed by Fidler, the concept of tumour heterogenicity suggests that tumours are composed of heterogenous subpopulations of cells differing in immunogenecity, invasiveness, cellular growth kinetics, sensitivity to cytotoxic drugs and ability to metastasize. The local tumour environment may favour the development of more aggressive clones in the formation of metastases. Although the size of individual clones with metastasizing potential in a given tumour is significant, only a very small percentage of circulating cells lead to the development of metastatic colonies.

The events surrounding the initiation of local tumour invasion by epithelial tumours include a loss of cellular adhesion to surrounding tumour cells and basement membrane, invasion by malignant cells of the subjacent connective tissue by the production of cellular enzymes and growth mediators, cellular attachment to extracellular membrane molecules, neovascularisation and entry or exit from the circulation through the attachment to endothelial cell ligands. A repeat of this events occurs at the metastatic sites.

In the case of squamous cell carcinoma of the head and neck, malignant cells may progress from carcinoma is situ to microinvasive carcinoma, to a deeply invasive tumour with lymphatic metastasis. Interestingly a head and neck squamous cell carcinoma has the ability to manifest at both extremes of histopathological development in the same anatomic location. The critical step in the transition from carcinoma in situ to microinvasive carcinoma is the destruction of the basement membrane. This destruction is accomplished by production of specific proteolytic molecules by the tumour cells, including matrix metalloproteinases, collagenases and plasminogen activators.

Angiogenesis is the growth of new capillaries by sprouting from established vessels. In normal tissues, self-limiting angiogenesis is a part of reproduction and organogenesis in addition to wound repair and healing. Conversely, pathological angiogenesis is not auto regulated, but results

from alterations in growth control mechanisms of disease process. Various tumour derived factors (eg, prostaglandin E2,platlet-derived growth factor, transforming growth factor-beta, transforming growth factor-alpha, beta-fibroblast growth facto)are still being investigated for their propensity to facilitate endothelial cell proliferation.

Recent research looking specifically at the production of cytokines regulating immune, inflammatory and angiogenetic response in patients with laryngeal squamous cell cancer has revealed higher serum concentrations of the cytokines interleukin-6,interleukin-8 and vascular endothelial growth factor. These agents may be important in proinflammatory and proangiogenetic responses of tumour cells.

The ability of a tumour to stimulate an angiogenic response should directly determine the capability of a tumour to metastasize and ultimately kill the host. The literature notes conflicting reports regarding microvessel density and nodal metastasis in head and neck squamous cell carcinomas. Tumour sites of varying origins with different vascularisation patterns at their primary sites may behave differently. Malignancies of the head and neck especially head and neck squamous cell carcinomas are the result of a series of genetic misadventures of squamous epithelial cells leading to malignant transformation. Variable genetic susceptibility, prolonged tobacco and alcohol exposure, viruses and immune suppression all can facilitate these genetic derangements.

Tumours invade local connective tissue by the production of proteinases and the expression of surface markers that facilitate attachment to extracellular matrix components. Tumor growth and size being limited by available nutrients from the surrounding milieu, recruitment of host capillaries leads to the formation of an intramural blood supply. Capillary lymphatic invasion by tumour cells allow malignant cell dissemination and the establishment of histologically identical tumours at distant sites.

Most recently, the expression of vascular endothelial factor-D in a mouse tumour model was found to lead to the lymphatic spread of tumour cells, tumour angiogenesis and tumour growth.

The dissemination of tumour cells beyond the primary site unfortunately remains the most significant factor in prognosis.

LYMPH NODE AND TUMOUR IMMUNITY

An early event in the metastatic process is the detachment of cancer cells from the parent tumour. Because a tumour has no primary lymphatics, cancer cells presumably gain access to the lymphatic system through the clefts between the lymphatic endothelial cells at the invasive tumour periphery. Once inside the lymphatic channels, cells are carried by the afferent lymphatics to the regional nodes where they lodge and proliferate.

The permeation theory of metastasis introduced by Handley in 1907 was based on autopsy studies of patients who had died of breast cancer and melanoma. He concluded that lymphatic metastasis originated by continuous permeation of lymphatics radiating away from the primary tumour site. The permeation concept of lymphatic metastasis was the basis for the development of in continuity (en bloc) dissection of nodes with primary cancer for head and neck.

Von Recklinghuasen noticed that metastasis could be found in the lymph glands when tumour did not involve the intervening lymphatics, and the embolic spread of metastasis is now generally accepted.

Handley's concept of permeation still applies to some clinical situations; generally recurrent cancer with obstruction of the normal lymphatic pathways leading to retrograde spread and tumors in certain sites such as large floor of mouth tumours with direct extension to the submandibular area. Previously untreated primaries even if massive seldom involve the neck by direct extension.

In the past it was believed that regional lymph nodes behave as traps against tumour cell dissemination. This 'Filter Barrier' hypothesis proposes that regional lymph nodes serve as mechanical and biologic filters in which phagocytosis assists the more mechanical phase of particulate trapping. In various studies, it has been shown that cancer cells

can traverse nodes that themselves are free of tumour, implying that the node is an ineffective barrier.

Fischer and Fischer reported that nodes were able to trap 90%of infused red blood cells and 40% of carcinoma cells. The nodes did not become saturated. Some studies have shown that nodes are potential barriers to infused tumour cells for only a limited time-approximately 3 weeks. Thereafter the tumour cells are no longer effectively retained.[9,10]

In a study it has been shown that as the primary tumour increased in size the number of cells in the nodes remained constant. The authors concluded that the nodes had a reasonably constant holding capacity and that above such a threshold, all other tumour cells passed on into efferent channels and the general circulation.[11]

Although the role of regional lymph nodes as a barrier to cancer spread and as a possible site of antitumour immune response is putative and remains to be established, majority of the workers are of the opinion that some sort of dynamic interaction does occur when tumour.

Emboli encounter lymphocytes within the nodes of head and neck cancer patients. The regional nodes are felt to be important for the initiation of systemic immunity to cancer cells, especially to weekly antigenic tumours. Patients who do not become positive for nodes at any time are thought to have immune competence that is entirely able to eliminate disseminated tumour cells in the nodes and elsewhere

throughout the body. Conversely the positive lymph node may denote either a failure of the above mechanism, or a change in the biologic nature of the tumour cells, or that the number of disseminated tumour cells have exceeded the capacity of the node for cell destruction.

The existence of an enlarged node does not necessary indicate the presence of metastatic spread, especially if the node is soft. In this case it may represent no more than a coincidental infection or the mounting of an immunological reaction within the node.

However just as this is true, it has been estimated that a node smaller than 1 cm is impalpable and yet may contain $10^6 – 10^7$ tumour cells. The principal problem for the clinician is how to decide whether a node which is palpably enlarged is involved with metastasis or not. At present such a decision remains purely clinical. Some authors have recommended that any enlarged palpable node in the drainage area of a histologicaly proven primary should be considered as metastatic until otherwise proved. Lindberg (1972) defined a clinically positive node as one which is greater than 1cm in size, spherical rather than a flat ovoid in shape and harder in consistency than a non metastatic node.

Throughout this study the above criteria of Lindberg was used to differentiate a metastatic from a non metastatic node.

THEORIES FOR THE OCCULT PRIMARY

It has been hypothesized earlier that the patient with malignant cervical lymphadenopathy but unknown primary site may in fact have no upper aerodigestive tract primary site. Rather the tumor primary developed in the neck within squamous cells remaining as remnants of brachial cleft cysts. Although this theory is intriguing, little evidence has been presented to support it and it has largely fallen out of favour.

The other theory is that these patients have exhibited spontaneous regression of the primary tumor site with persistence of cervical metastasis. Unfortunately there is no evidence for the spontaneous regression of squamous cell carcinoma.

Current theory is that unknown primary tumours are likely to be, primary tumours that exist in the upper aerodigestive tracts or skin, but subclinical at the time of presentation. Thus unknown primary tumours remain undetected but are presumed to be present. Anecdotal support of this theory includes the identification of some of the primary tumours during or after treatment.

HISTOLOGICAL GRADE OF THE TUMOUR AND ITS INFLUENCE

Histologically a squamuos cell carcinoma consists of an admixture of normal squamous cells and atypical anaplastic squamous cells. The more malignant the tumour, the greater is the number of atypical cells .The

atypicality expresses itself in terms of variation in the size and shape of cells, hyperplasia and hyperchromatasia of the nuclei, absence of intercellular bridges, atypical mitotic figures, and keratinisation of cells.

Differentiation in a squamous cell carcinoma takes place in the direction of keratinisation, and so the degree of keratinisation represents the essential feature in the system of histological grading introduced by Broder (1921).This grading system recognizes four grades of severity according to the proportions of differentiated cells present in the tumour.

- Grade I - more than 75% of the cells are differentiated
- Grade II – between 50% to 75% of the cells are differentiated
- Grade III – between 25% to 50% of the cells are differentiated
- Grade IV – less than 25% of the cells are differentiated.

Alternatively squamous cell carcinoma can be graded as

1. Well differentiated – tumours with minimal pleomorphism, few mitoses, large number of horn pearls and abundant keratinisation.
2. Moderately differentiated – tumours where typical cells are conspicuous, few horn pearls are present and keratinisation is much less evident.
3. Poorly differentiated – tumours with much cellular and nuclear pleomorphism, negligible keratinisation and absence of horn pearls[12].

The relevance of histologic grade of tumour to prognosis is well established .Arthur and Farr (1972) studied the prognostic significance of histologic grade in squamous cell carcinoma of oral cavity and oropharynx and demonstrated a clear relationship between the histologic grade and metastatic nodal disease, stage of the disease and cure rate. They noted a proportionate increase in nodal involvement with increasing histologic grade of the tumour and suggested that histologic assessment should play a part in designing the therapeutic approach[12].Other authors have also appreciated the usefulness of histologic grading as a clue to overall prognosis[13].

TNM STAGING

The current classification was proposed by the American Joint Committee for Cancer Staging and end results reporting in 2002[1] and is being widely adopted.

In this classification, the recommended tumour (T) designation varies from one anatomic region of the head and neck to another, but the node (N) and distant metastasis (M) categories is applicable to all of the areas of the head and neck. Stage grouping based on the TNM stage is also similar throughout the head and neck.

The (N) and the (M) categories as well as the stage grouping, which are constant for all the head and neck regions are discussed first.

N –Classification of all head and neck cancers (AJCC,2002)[1]

- N_x - nodes cannot be assessed.
- N_0 - no clinical positive nodes.
- N_1 – single clinically positive homolateral node less than 3cms in diameter.
- N_2 –single clinically positive homolateral node 3-6cms in diameter, or multiple clinically positive homolateral nodes none over 6 cms in diameter.
    1. N_{2a} – single clinically positive homolateral node 3-6cms in diameter.
    2. N_{2b} – multiple clinically positive homolateral node none over 6cms.
- N_3 –massive homolateral nodes any one node more than 6 cms, bilateral nodes or contralateral nodes .
    1. N_{3a} –clinically positive homolateral nodes at least one greater than 6cms in diameter
    2. N_{3b} – clinically positive bilateral nodes
    3. N_{3c} – only contralateral clinically positive nodes.

M - Classification of all head and neck cancers (AJCC,2002)

- M_x – metastasis not assessed
- M_0 – No known metastasis
- M_1 – Distant metastasis present

STAGE GROUPING OF HEAD AND NECK CANCERS (AJCC,2002)

Stage I – T_1, N_0, M_0

Stage II – T_2, N_0, M_0

Stage III - T_3, N_0, M_0

$T_{1,2,3}$, N_1, M_0

Stage IV_a – T_4, $N_{0,1}$, M_0

T_{1-4}, N_2, M_0

IV_b - Any T, N_3, M_0

T_{4b}, Any N, M_0

IV_c – Any T, Any N, M_1

The T – classification of the oral cavity and oropharyngeal tumour is described below (AJCC,2002)

- T_x – No available information on the primary tumour
- T_0 – No evidence of primary tumour
- T_{is} – Carcinoma in situ
- T_1 – Tumour 2cms or less in greatest diameter

- T_2 – Tumour 2 – 4 cms in greatest diameter
- T_3 – Tumour more than 4 cms in greatest diameter
- T_4 – Tumour more than 4 cms with invasion into contiguous structures such as floor of mouth, skin, muscles and bone.
- T_{4a} – Tumour involving cortical bone, deep tongue musculature, maxillary sinus, skin of face
- T_{4b} – Tumour involving maxillary plates, pterygoid plates, skull base, encases the internal carotid artery[7].

RISK FACTORS FOR HEAD NECK CANCER

It has been estimated that the use of tobacco and alcohol can account for up to 80 percent of cases of head and neck squamous cell carcinoma. Both act throughout the aerodigestive tract, contributing to the field cancerisation effect, and both can induce genetic alterations, such as mutations in the p53 tumour suppessor gene. Other factors which may play a role include viral infection, oocupational exposure, radiation, dietary factors and genetic susceptibility.

- **Tobacco**-there is an increased risk of head and neck squamous cell carcinoma from a 5-to-25 fold, in heavy smokers compared to nonsmokers[14].The relative risk in current tobacco users is 6.5.the relative risk increased with the duration of smoking and gradually declined after smoking cessation with no excess risk at 20

years[15].The age at onset of smoking (below 18 years of age) and duration of smoking (over 35 years) were high risk factors. Passive smoke exposure also may e a contributing factor. One report evaluated patients with head and neck squamous cell carcinoma who did not use tobacco, with rare exceptions, did not abuse alcohol. These patients had a significantly higher risk of exposure to environmental tobacco smoke in both the workplace and home than a control population without cancer. This relationship primarily occurred in women and those with tongue cancer.[16]

Epidemiologic studies have suggested that cigar smoking is associated with an increased incidence of head and neck squamous cell carcinoma[17] and smokeless tobacco with an increased risk of cancer of the tongue, oral cavity and pharynx.[18] Marijuana use may modestly increase the risk of cancer, an effect that is magnified by cigarette smoking.[19]

- **Alcohol** –although it is often difficult to separate the effects of smoking and alcohol, studies have consistently shown that alcohol consumption increases risk of cancer in the upper aerodigestive tract.[20] The relative risk of developing cancer appears to be dose dependant, ranging from 5.5(alcohol intake greater than 50g/day) to 33.8(alcohol intake greater than 120g/day) .Drinking liquor may be associated with greater risk than drinking only wine[21]. Moderate alcohol intake (10 to 19g/day) has no effect among nonsmokers.

The combined effect of alcohol and smoking is multiplicative, with the risk of developing Head and Neck cancer being as much as 200 times greater for heavy smokers and drinkers[22].

- **Epstein-Barr virus**-The strongest association between a virus and head and neck cancer is that of Epstein-Barr virus and nasopharyngeal carcinoma. EBV is the causative agent for oral hairy leukoplakia.
- **Human papilloma virus**- HPV type-16 has been detected in 8 to 36 % of head and neck cancer[23].It may contribute both by direct effects on proliferation and by increasing mutational frequency in the host cells. The prevalence of HPV infection appears to be site specific, and is highest in invasive tumours of the oropharynx and oral cavity[24].The presence of HPV appears to confer a better prognosis.
- **Occupational exposure** – These include asbestos, pesticides, polycyclic aromatic hydrocarbons, textile workers, wood workers, manufacturers of mustard gas, plastic and rubber products, naphthalene refineries, ethanol, sulfuric acid mist, leather and paint workers, automobile mechanics, construction workers(cement),metal workers and bartenders(passive smoking).Formaldehyde was classified as a carcinogen in 2004 because of its association with nasopharyngeal carcinoma and possibly cancers of the nasal cavity and paranasal sinuses.

- **Radiation** – Prior radiation for either malignant or benign disease has been linked to head and neck cancer.
- **Diet** – Risk of nasopharyngeal carcinoma is increased in frequent consumers of preserved meats which contain high levels of added nitrites[25].Increased risk of head and neck squamous cell carcinoma has also been associated with more frequent intake of eggs and red meat and a low carotenoid intake[26].
- **Genetic factors** – First degree relatives and siblings of patients with head and neck squamous cell carcinoma are more likely to develop upper aerodigestive tract cancer than controls[27].
- **Others** – Poor oral hygiene has been linked with carcinoma of oral cavity[28]. Lip cancer is seen in renal transplant recipient.

DIAGNOSTIC EVALUATION

A complete detailed history of the present and past illness with a thorough physical examination is a mandatory to the workup of the patient.

Laboratory studies are not typically used in the workup of a patient but are used to evaluate a patient's anaesthetic risk and to provide baseline laboratory data.

Serology of Ebstein-Barr virus has been shown to correlate with the presence of nasopharyngeal carcinoma[29].

Chest radiograph

Chest radiograph are taken for all patients. If any suspicious lesion found in chest radiograph then CT scan is indicated. If a lung neoplasm is found then it is evaluated separately.

CT scan

The neck CT scan is important in the search for an occult primary site and also to evaluate the extent of nodal disease, to check for obvious extra capsular spread and soft tissue involvement and examine for suspicious nodes in the contralateral neck. Contrast enhanced CT from the base of the skull to the level of the thoracic inlet is indicated. CT can identify tumours of the head and neck based upon either anatomic distortion or specific tumour enhancement. In general tumours enhance more than any normal head and neck structures except mucosa, extraocular muscles, and blood vessels [30]. A radiologically heterogenous appearance or the presence of central low attenuation may indicate pathologic lymphadenopathy, even in small lymph nodes.

MRI scan

MRI has multiplanar capabilities, it provides superior soft tissue contrast and it can identify early evidence of dural involvement or perineural invasion [31]. It is therefore useful for assessment of local spread of nasopharyngeal carcinoma and sinonasal carcinoma. MR Angiography can generate images of large arteries and veins noninvasively without the

use of IV contrast. This is reserved for cases where tumour is thought to encase a major vessel.

PET scan

Usefulness of PET scanning is still evolving. Potential clinical applications for the PET scanning include improved pretreatment staging, identification of an occult primary site, estimation of treatment response and differentiation of early recurrence from scar tissue[32] . Many incorporate this imaging modality in their diagnostic evaluation for an occult primary tumour. Tumour cells have a higher metabolic rate than normal tissue; head and neck neoplasms have an increased glycolytic rate. Thus head and neck neoplasms are good candidates for metabolic imaging and can be traced using a glucose analog, 2-[fluorine-18]fluoro-2deoxy-D-glucose. (FDG).

FDG uptake reflects cellular metabolism and cellular processes such as infection, neoplasm or inflammation. They are characterized by increased metabolic activity and consequent accumulation of the FDG tracer. This accumulation which appears as hot spots on PET imaging may help to localise an unknown primary tumour.

The Danish study demonstrated that FDG PET detected a primary tumour in 24% of patients with metastatic cervical adenopathy and otherwise negative clinical and radiological evaluation.

The key limitation of PET has been the size of tumour it can detect. Commonly available PET scanners may have a resolution of approximately 1cm.That is they will inconsistently detect lesions smaller than this size. New PET have resolution of 5mm.An additional limitation of PET scanning has been the anatomically nonspecific image produced by these scanners. Hot spots appear as general regions without good borders. So whereas it may be possible to state for eg; that left side of the base of the tongue appears 'hot', any additional information regarding the size or localization would be inaccurate.

Newer scanners that supplement PET with CT fusion techniques are becoming available. These machines can overlay the images so that the hot areas are visible as coloured halos over the CT scan image, greatly facilitating the accuracy and localization of the PET technology.

Panendoscopy of the upper aerodigestive tract with biopsy samples obtained from suspicious areas should be done.

Mucosal biopsies of nasopharynx,fossa of rosenmuller, tonsils, pyriform sinus, hypopharynx, vallecula, postcricoid region and base of tongue should be done routinely for all patients with unknown primary.

Previous studies have suggested that the most common sites of primary tumour detected on panendoscopy were the nasopharynx and hypopharynx. In a recent University of Florida study, the most common

sites of primary cancer detected seen now to have shifted to include the tonsillar fossa or the base of the tongue[33] .

Because the tonsil remains a common site of primary tumour , most clinicians advocate tonsillectomy in addition to directed biopsies in the workup of an unknown primary tumour. Questions regarding whether random tonsil biopsies or tonsillectomy should be performed in the evaluation of an unknown primary site and whether such tonsillectomy should be ipsilateral or bilateral tonsillectomy continue to be controversial.

In a 1998 study at john Hopkins hospital McQuone et al demonstrated that the detection rate of occult tonsillar carcinoma is increased by performing tonsillectomy rather than focal tonsillar biopsy. Although only 13% of tonsillar biopsy specimens were positive for squamous cell carcinoma, 39% of the patients undergoing bilateral tonsillectomy for workup of unknown primary site was found to have squamous cell carcinoma within tonsil. Furthermore one patient was found to have squamous cell carcinoma in both tonsils, strengthening the argument for bilateral tonsillectomy. Bilateral tonsillectomy does not significantly increases the morbidity associated with unilateral tonsillectomy and eliminates the asymmetry that can confound follow up examination after a unilateral procedure [34].

TREATMENT

Several different treatment strategies are available for the management of the true unknown primary site and squamous cell carcinoma metastatic to the neck. Whether radiation therapy is sufficient treatment for control of neck disease and whether potential primary sites should be irradiated or simply followed are controversial. Additional controversy focuses on whether radiation should be offered to patients pre- or postoperatively. Finally, questions have surfaced about whether the contralateral neck needs to be treated. Which treatment strategy provides best outcome remains a subject of debate in the literature.

In discussing treatment strategies, it is important first to have an understanding of prognostic factors. In all large series, lymph nodal stage has correlated with outcome. Supraclavicular lymph node metastases are more likely to be associated with disease below the clavicles, and hence, are associated with poorer survival. Histologic extracapsular spread has been noted to affect survival adversely in most large series as well. As might be expected, more primary sites were identified in patients treated with surgery than in patients treated with radiation. Although treatment protocols may vary by institution and clinical bias, there is consensus that advanced nodal disease and extracapsular spread necessitate more aggressive therapy[35].

For a few patients presenting with N1 or N2a disease, single modality therapy is a reasonable approach. Acceptable courses of

treatment include neck dissection alone, radiation alone, and neck dissection plus radiation if extracapsular spread is noted on histopathologic analysis. A 1998 review from M.D.Anderson recommends that patients with N1 or small mobile N2a disease be treated with neck dissection alone and that postoperative radiation therapy be reserved for cases of extracapsular spread, multiple nodes or connective tissue invasion[36]. The 5-year disease free survival rates were 85% in patients with a solitary node and 58% for patients with multiple nodes. Similarly, in patients who have undergone an excisional biopsy of a solitary node, the neck may be treated with radiation alone with a 95% likelihood of neck control. Thus single modality treatment in patients with N1 or N2a disease is reasonable .For patients with disease beyond N1 or N2a combined modality therapy is recommended.

Patients with more advanced disease, in contrast are triaged into an arm of treatment that includes both surgery and radiotherapy. The timing of radiotherapy is also a source of controversy. Proponents of preoperative radiation therapy argue that surgical complications delay the initiation of radiation therapy, target tissues are theoretically better oxygenated in the preoperative state, and radioresistant primary tumours may become evident over the course of radiation therapy and can be removed with one definitive surgical procedure if radiation therapy is implemented before the planned neck dissection[34].

Proponents of postoperative radiation therapy argue that a neck dissection before radiotherapy allows improved delineation of disease extent and better staging through pathologic evaluation of the neck dissection specimen[37]. Although adjuvant chemotherapy has shown mixed results, it is often recommended in cases of inoperable disease or with distant metastases. There is some evidence that concurrent chemotherapy and radiotherapy in the postoperative setting improve locoregional control rates.

The decision to include suspected primary sites in the radiation field also remains controversial. Certainly the challenge facing the clinicians is deciding how to maximize the chance of survival while minimizing the treatment morbidity. Review of the literature reveals a trend toward treating both the ipsilateral and contralateral necks as well as potential mucosal primary sites. Certainly many of the primary sites (base of tongue, nasopharynx, supraglottis) are known for their bilateral nodal drainage. Tong et al[38] point out that treatment limited to the involved side of the neck alone may compromise further radiation therapy should a primary mucosal site emerge. For this reason, bilateral radiation to the neck and mucosal sites is recommended.

Debate continues to center around which portals should be included in the radiation therapy. The consensus seems to be that the oral cavity and a laryngeal strip can be excluded, but the base of the tongue,

hypopharynx, and supraglottic sites should be included[39]. The decision to include the nasopharynx should be based on whether metastases are high and posterior and whether demographic factors suggest that the patient is at high risk for a nasopharyngeal primary site. Sparing the oral cavity and of an anterior strip approximating the anterior true vocal cords may significantly decrease the morbidity of the mucosal irradiation.

Regarding ipsilateral versus bilateral treatment of the sides of the neck, Carlson et al[40] demonstrated that the rates of local control for ipsilateral and bilateral neck irradiation were 53% and 90% respectively. Reddy et al[41] also reported a series comparing ipsilateral radiotherapy with radiation delivered to both sides of the neck and sites of mucosal primaries. Significantly better neck control was demonstrated in the group receiving radiation to both sides of the neck and mucosal sites.

Finally, recent discussion has focused on the extent of neck dissection indicated in the patient with a cervical metastasis and unknown primary lesion. A growing body of evidence suggest that a selective neck dissection including the involved level and contiguous levels with appropriate sacrifice of the involved structures is reasonable. Appropriate use of selective neck dissection can minimize the postoperative morbidity associated with modified and radical neck dissection without compromising neck control and survival[42].

Even with advances in treatment protocols, the overall survival for squamous cell carcinoma metastatic to a cervical node with an unknown primary site remains approximately 50%.The 2-,5- and 10 year disease specific survival rates have been reported to be 82%,74% and 68% respectively. Nodal stage has been shown to be significantly associated with disease specific survival.

CHEMOTHERAPY

The role of chemotherapy in head and neck cancer is expanding and its utility varies with the stage of the disease. For patients with metastatic or incurable locoregional disease chemotherapy is palliative. In contrast for patients with potentially curable locoregional head and neck cancer, chemotherapy is an integral part of multimodality approach. In such cases chemotherapy may be administered as induction therapy, concomitant with radiotherapy or with a combined approach.

Single agent chemotherapy

Several cytotoxic chemotherapy drugs have significant activity in advanced head and neck cancer when administered as a single agent. Direct comparisons of efficacy are limited by the paucity of randomized trials, and this complicates the establishment of recommendations for standard of cure. Although most patients will be treated with combination chemotherapy, occasionally single agents may be used for palliation.

The choice of agents depends in part upon the patient's clinical status and the ability to tolerate drug-specific side effects. Acceptable drugs include paclitaxel, docetaxel, methotrexate, cisplatin, carboplatin, ifosfamide and 5-Fluorouracil.

In advanced squamous cell head and neck cancer, the taxanes have emerged as perhaps the most active of all single agents.

General principles of combination chemotherapy

Many combination chemotherapy regimens have been studied for the treatment of advanced head and neck cancer. Prior to mid 1980s, the most aggressive regimens included methotrexate and generally consisted of combinations of two or four drugs, often methotrexate plus cisplatin, bleomycin, 5-FU or vincristine. These regimens have been largely replaced by three categories of drug combination:

- The combination of a platinum analog (cisplatin or carboplatin) and 5-FU.
- The combination of a platinum analog and a taxane (paclitaxel or docetaxel).
- The combination of a taxane, a platinum analog and 5-FU with or without leucovorin.

Recommendations for combination chemotherapy for advanced head and neck cancer.

For metastatic or recurrent disease, any of the several regimens may be used. Since none has been proven yet to prolong survival, care must be exercised to avoid major acute or chronic toxicities and consideration should be given to single agent therapy.

For patients with good performance status, appropriate combinations include cisplatin or carboplatin plus 5-FU, or platinum analog plus a taxane.

NEW THERAPIES UNDER INVESTIGATION

Monoclonal antibodies

Cetuximab- The majority of head and neck cancers over express endothelial growth factor, making them a good target for cetuximab, an anti-EGFR monoclonal antibody that inhibits receptor activity by blocking the ligand binding site. In addition to being investigated as a single agent and in combination with cytotoxic chemotherapy, cetuximab is also under study as a radiosensitiser.

Other potential agents that block the activation of EGFR are the tyrosine inhibitors such as geftinib and erlotinib.

Gene therapy

Gene therapy utilize a vector to deliver genetic material to a cell in an attempt to alter its biology via expression of the delivered gene. The majority of effort has been aimed at modification of p53.The p53 gene is

inactivated in approximately one half of squamous cell head and neck cancers.

ONYX-015 – It is an adenovirus containing a deleted E1B 55-kDa gene, which actively replicates in, and lyses p53-deficient cells.

RPR/INGN 201 – It utilizes a replication deficient adenovirus to deliver a cytomegalovirus promoter and a wild type p53 gene.

Cisplatin/epinephrine injectable gel – for patients with refractory or multiply recurrent local tumour involvement, a novel strategy is direct application of cisplatin into the tumour itself.

RADIOTHERAPY

Radiation may be given as a once daily treatment or hyper fractionated (twice daily).It may be continuous (five days per week without interruption) or given in a split course (every other week or three weeks on with a one or two weeks break followed by three more weeks of treatment).

NECK DISSECTION

Introduction

Cancers in the head and neck region commonly metastasize to cervical lymph nodes. The term neck dissection refers to a surgical

procedure in which the fibro fatty contents of the neck are removed for the treatment of cervical lymphatic metastases. Neck dissection is most commonly employed in the management of cancers of the upper aerodigestive tract. It is also used for malignancies of the skin of the head and neck area, the thyroid, and the salivary glands.

Radical neck dissection has been the standard surgical procedure for treatment of metastatic neck cancer since its description by Crile in 1906. Until only a couple of decades ago, it was widely used as an elective procedure for occult neck disease and as a therapeutic procedure for clinically manifest nodal metastases. However, in the last 2 decades, a shift toward the use of more conservative surgical procedures has occurred, arising from the realization that many non lymphatic structures in the neck, as well as certain lymph node groups, may be preserved in certain situations without compromising disease control.

Experimental studies of lymphatic drainage and clinical studies of nodal distribution have enabled reliable prediction of the lymph node groups most likely to be involved with metastatic disease for different locations of the primary tumor. Importantly, establishing which lymph node groups carry negligible risk of involvement and may be safely preserved is also possible. As a result, a great variety of surgical procedures have now been described for use in varying clinical situations.

The current classification of neck dissections by the American Academy of Otolaryngology / Head and Neck Surgery is based on the following governing principles:

- Radical neck dissection is the standard basic procedure for cervical lymphadenectomy, and all other procedures represent one or more modifications of this procedure.
- When modification of the radical neck dissection involves preservation of one or more non lymphatic structures, the procedure is termed a modified radical neck dissection.
- When the modification involves one or more lymph node groups that are routinely removed in the radical neck dissection, the procedure is termed a selective neck dissection.
- When the modification involves removal of additional lymph node groups or non lymphatic structures relative to the radical neck dissection, the procedure is termed an extended radical neck dissection

This classification was developed by the Committee for Head and Neck Surgery and oncology, American Academy of Otolaryngology – Head and Neck surgery, Courtesy of the Archives of Otolaryngology – Head and Neck Surgery.

- Radical neck dissection
- Modified radical neck dissection
- Selective neck dissection
    - Supraomohyoid type
    - Lateral type
    - Posterolateral type
    - Anterior compartment type
- Extended radical neck dissection.

Radical neck dissection

Originally described by Crile in 1906, this procedure is an en bloc clearance of all fibro fatty tissue from one side of the neck, including the lymph nodes from level I through V, lymph nodes[43]. Surrounding the tail of the parotid gland, the spinal accessory nerve, the internal jugular vein, and the sternocleidomastoid muscle. It does not include the removal of the postauricular, suboccipital, perifacial buccinator, retropharyngeal and central compartment nodes.

Previously used for neck disease of any stage, from microscopic to bulky nodal disease, this procedure now finds its application limited to patients with advanced neck disease or with gross extracapsular spread to

the spinal accessory nerve, sternomastoid muscle and the internal jugular vein.

Modified radical neck dissection

This operation involves the removal of the same lymph node groups as the radical neck dissection (levels I through V) but requires preservation of 1 or more of the 3 non lymphatic structures; the spinal accessory nerve, the internal jugular vein, and the sternomastoid muscle.

Modified neck dissection is indicated in cases with clinically palpable metastatic neck disease. Conversion to the radical neck dissection becomes necessary when gross involvement of the nerve, vein and muscle is present, although the involvement of all 3 is unusual, except in very advanced (N3) disease.

Comprehensive neck dissection is a term that frequently appears in the literature. This refers to any type of neck dissection that involves removal of lymph nodes from levels I through V and corresponds, therefore, to radical and modified radical neck dissections according to the Academy's classification.

Selective neck Dissection

This term refers to a type of neck dissection in which certain lymph node groups in the neck are preserved while others are removed. Included in this category are supraomohyoid neck dissection, lateral neck

dissection, anterior compartment neck dissection, and posterolateral neck dissection.

Supraomohyoid neck dissection

Selective removal of the level I, II and III lymph nodes is called supraomohyoid neck dissection. The operation includes the resection of soft tissue in the submental triangle, along with the submandibular triangle contents, including the submandibular gland and the fibrofatty tissue along the internal jugular vein in the upper 2 levels. The dissection contents include the fascia covering the medial aspect of the sternomastoid muscle; the muscle itself is retracted laterally and preserved. These neck contents are peeled off from the internal jugular vein and from around the accessory nerve, sparing these structures.

Supraomohyoid neck dissection is indicated for the prophylactic treatment of occult neck disease in cancers known to metastasize to this group of nodes, i.e cancers of the oral cavity. Application of this type of the neck dissection to treat clinically positive nodes remains controversial. If this operation is performed for N+ disease, including level Ic in the dissection may be prudent.

Lateral Neck dissection

Selective removal of the soft tissues containing the level, II, III and IV lymph nodes along the internal jugular vein is called lateral or anterolateral neck dissection. The spinal accessory nerve, sternomastoid muscle, and internal jugular vein are spared in this operation.

This operation is commonly performed for the prophylactic treatment of occult disease in patients with primary cancers in the oropharynx, hypopharynx, or larynx. Its application in the N+ situation is still under investigation.

Both the supraomohyoid and the lateral neck dissections may need to be performed on both sides in patients whose primary tumors are located close to or across the midline. Cancers of the central tongue, floor of the mouth, low lip, and supraglottic larynx are known to metastasize bilaterally.

Anterior compartment neck dissection

This operation involves excision of the level VI lymph nodes. The procedure is indicated for the treatment of cancers of the thyroid gland, hypopharynx, cervical trachea, cervical esophagus, and subglottic larynx. The boundaries of the dissection are the hyoid hone superiorly, the suprasternal notch inferiorly, and the carotid sheaths on either side. Hyopoparathyroidism may be a disabling complication if care is not taken

to identify and preserve the parathyroid glands, and injury to the parathyroid blood supply is a risk with this procedure. Excising and reimplanting the glands into the sternomastoid or pectoralis major muscles may be necessary. Alternatively, the dissection may be limited to one side if the lesion is not close to the midline, particularly if radiation therapy can be administered postoperatively.

Posterolateral neck dissection

Posterolateral neck dissection was initially described by Rochin in 1962 and later modified and popularized by Geopfert et al for use in patients with cutaneous malignancies of the scalp and postauricular and suboccipital regions. Unlike all other neck dissections, this operation is performed with the patient in the lateral decubitus position and consists of an en bloc removal of the lymph nodes in the suboccipital, postauricular, and upper, middle and lower jugular nodes, along with posterior triangle nodes situated superior to the accessory nerve. Although the original description included sacrifice of the accessory nerve, internal jugular vein, and a portion of the trapezius muscle, Diaz et al from the MD Anderson Cancer centre showed in 1996 that preserving these non lymphatic structures dies not increase the failure rate of this operation.

Extended neck dissection

In cases of advanced neck disease, certain lymphatic or non lymphatic structures, not routinely included in the aforementioned neck dissections, may have to be removed. Extended neck dissection is the term used to describe these procedures. Retropharygeal lymph nodes, the hypoglossal nerve, portions of the prevertebral musculature, or the carotid artery are some of the structures that may occasionally have to be excised in order to obtain negative margins.

MATERIALS AND METHODS

During a period of 29 months from august 2004 to february 2006 datas were collected from 156 patients who were admitted to the surgical units of coimbatore medical college hospital with a diagnosis of cervical lymphadenopathy. Children below 12 years of age were not included. All patients with known primaries were excluded from the study. Likewise patients with lymphatic malignancies were excluded. Patients with infective pathology and non specific lymphadenitis were also excluded from the study. A total of 85 patients were finally included in the study.

The workup for all the patients on admission was a follows:

History

A detailed history was obtained from all patients, attention was focused on onset of swelling, duration of swelling ,rate of growth of the swelling ,associated pain, pressure and obstructive symptoms like dizziness (carotid tree involvement),shooting pain over arm (brachial plexus involvement), difficulty in breathing ,difficulty in swallowing, change in voice were elicited. History of otalgia, aural fullness, nasal congestion and epistaxis were also obtained. Social history including occupational hazards like exposure to ultraviolet light, industrial chemicals and metals were obtained. Information concerning alcohol consumption and tobacco

product usage were obtained. History of any irradiation to the head and neck in the past and past treatment of other head and neck carcinoma were elicited. Any associated illness were also noted.

Physical examination

The lymph node was taken significant if the size was more than 1cm, spherical rather than ovoid in shape, hard in consistency.

Note was made of the side and the triangle of the neck involved, the total number of palpable nodes, the groups involved, size, consistency, presence of tenderness, fixity to skin as well as deeper structures, presence of any contralateral nodes and the N stage of the nodes.

Nodes deep to the sternocleidomastoid were included in anterior cervical triangle as the classical description of the cervical triangle excludes the nodes deep to the sternomastoid muscles from either of the two triangles. Midline nodes were considered as homolateral nodes. In all instances the clinical impression of the first observer was confirmed by at least one another observer.

The physical examination was then focused on the head and neck, beginning with inspection and palpation of the skin. The scalp and external ears were inspected in detail. All zones of the neck were palpated thoroughly in an effort to find additional lymphadenopathy or masses. The nasal vestibule, oral cavity and oropharynx were thoroughly inspected.

Because submucosal lesions are not typically evident with visual inspection, manual palpation of the oral cavity and the oropharynx were done. Special attention was paid to the base of the tongue during palpation. Special focus was given for any thyroid swelling, breast, respiratory system, abdomen, and genitalia were examined.

Chest radiograph was done for all patients. For patients with suspicious lesions on chest radiograph, CT scan of the chest was done. Bronchoscopy was done for all patients

Indirect laryngoscopy was done for all patients particularly looking for any growth or mucosal abnormalities in nasopharynx, oropharynx and larynx.

Upper gastrointestinal endoscopy was done for all patients. Ultrasound abdomen was done for all patients.

FNAC was done from the nodes. The histopathological report was expressed in three grades –Well differentiated, moderately differentiated and poorly differentiated carcinoma, adenocarcinoma and papillary carcinoma thyroid.

RESULTS OF THE STUDY

1. AGE DISTRIBUTION

Incidence of age in nodal metastasis of neck with unknown primary

Table - 1

Age in years	No of cases out of 85	Percentage %
10-20	1	1
20-30	4	5
30-40	9	11
40-50	15	17
50-60	28	33
60-70	16	19
70-80	8	9
> 80	4	5

The overall age incidence for patients with head neck secondaries with unknown primary was in the range of 19-84 years with a mean of 52 years. Most cases presented around 30-80years. Among the 5 cases presented below 30years 3 cases had papillary carcinoma thyroid

2. SEX DISTRIBUTION OF THE NODES

Sex distribution of the nodes

TABLE - 2

sex	No of cases out of 85	Percentage%
Male	70	82
Female	15	18

Out of the 85 patients with neck secondaries with unknown primary 70 (82%) patients were male, 15(18%) patients were female.

The following were the histopathological distribution among males and females;

TABLE - 3

Histolopathology	males	Females
Poorly diff carcinoma	47	9
Mod diff carcinoma	2	1
Well diff carcinoma	14	1
Adenocarcinoma	2	1
Papillary ca thyroid	5	3

3. TOPOGRAGHICAL DISTRIBUTION OF NODAL METASTASES

Analysis of topographical distribution of cervical node metastasis from various sites revealed the following patterns.

46 patients (54.2%) presented with more than one group of nodes. Of these most of them were in the level II and level III.

23 patients (27%) patients presented with bilateral nodes. Most of these patients had nodes in level II, level III and level IV.

39 patients (45.8%) presented with only single group of nodes. The following pattern was noted in these patients.

Out of the 39 patients who had a single group of nodes 74% had the nodes in level II and level III.

Topographical distribution of nodes

TABLE - 4

Lymph node levels	No of patients out of 39	Percentage
Level I	0	0
Level II	13	33.3
Level III	16	41
Level IV	6	15.3
Level V	4	10.2
Level VI	0	0

Of the 39 patients who presented with single node only, most of them were in level II, III and level IV.

No patients presented with level I and level VI nodes with an unknown primary.

4.SIDE OF DISTRIBUTION OF THE NODES

TABLE - 5

Side distribution of nodes

Side of the nodes	No of patients out of 85	Percentage
Left	33	39
Right	52	61

Of the 85 patients most of them(52 patients-61%) presented with right sided nodes.33 patients(39%) presented with left sided nodes

The following are the histopathological distribution of nodes

TABLE - 6

Histopatholgy	Right	Left

Poorly diff carcinoma	36	20
Mod diff carcinoma	3	-
Well diff carcinoma	9	6
Adenocarcinoma	2	1
Papillary ca thyroid	2	6

5.HISTOPATHOLOGICAL ANALYSIS OF THE NODAL METASTASIS

Out of the 85 patients included in the study 56 patients(66%) had poorly differentiated carcinomatous deposit .15 patients (18%) had metastatic deposit from squamous cell carcinoma.

The histopathological analyses are presented in the following

TABLE - 7

Histology	No of patients	Percentage
Poorly differentiated metastatic carcinoma	56	66
Moderately differentiated metastatic carcinoma	3	3.5
Metastatic deposit from squamous cell carcinoma	15	18
Metastatic deposit from adenocarcinoma	3	3.5
Metastatic deposit of papillary carcinoma of thyroid	8	9

TREATMENT

All patients with operable nodes were treated with radical neck dissection. Those patients with extracapsular spread and multiple nodes were given radiotherapy and chemotherapy. For patients with operable bilateral nodes bilateral radical neck dissection was done in intervals.

For patients with inoperable masses chemoradiation was given.

Combination chemotherapy with cisplatin (Days 1- 2) and 5-FU(for Days 1- 5) was regimen given for all the patients.

Radiotherapy was given for 33 fractions of 300cGY per day for 5 days/week. A total dose of 6600 cGy was given. Palliative radiotherapy was given for advanced disease with 10 fractions of 200cGY per day. A total of 2000 cGY was given.

For patients with papillary carcinoma thyroid, total thyroidectomy with central neck dissection was done with radical neck dissection on the side of the lesion.

During the 29 months study no subsequent primary site was identified in all the patients.

DISCUSSION

Squamous cell carcinoma of the head and neck is the most common malignancy in India. Treating a patient with malignant cervical lymphadenopathy poses a challenge to the clinician in finding out the primary site.

- The incidence of malignant cervical lymphadenopathy in our studty was 2 % of all cancers.
- The male to female ratio is 4:1 in our study, which matches with the world average[44]. The higher incidence in the males could be due to increased exposure to tobacco products and occupational hazards than females.
- The mean age in our study was 49 years for all types of malignant cervical lymphadenopathy with unknown primary, which is a decade earlier than western average[44]. 80% of the patients presented between 30- 70 years. Highest incidence was seen between 50 – 60 years.
- 66% of the patients had poorly differentiated carcinoma and 18% of the patients had well differentiated squamous cell carcinoma. This is

in contrast to the western literature where squamous cell carcinoma accounts for 30% -50% and poorly differentiated carcinoma accounts for 25%. This could imply that more aggressive cancers are seen in our part of the world. This could be due to variable disease process or the various pathogenic factors playing a part.

- 27% of the patients presented with bilateral nodes, which means the most probable site of primary could be in the midline structures like base of tongue, nasopharynx and supraglottis.
- In our study we also noted a higher incidence on the right side(61%), when compared to the left side(39%). Are they due to keeping the tobacco products more commonly on the right is to be evaluated by further studies.
- Out of 8 patients (9%) of papillary carcinoma thyroid 5 patients (62.5%) were male and 6 patients (75%) presented on the left side.
- Of the 85 patients only 2 patients were from Christian community. The rest of them were from the Hindu community. This difference could be due to population ratio or social habits that are common in some communities. Is this a significant finding has to be evaluated by further studies.

CONCLUSION

The unknown primary tumour presents several clinical dilemmas including how to find the primary site and, if the site is never found, to direct treatment.

The incidence of patients with an unknown primary site is low overall because of the effectiveness of clinical examination coupled with pan endoscopy and directed biopsies. Radiograghic technology including CT/MRI, PET scan, and more recently,PET-CT may be of value in some cases. As these diagnostic methods become more refined there may eventually be no patients with an unknown primary tumour. Of course, once the primary site is identified, treatment of this patients can become much more specifically directed. We hope that in future the unknown primary site will no longer be a featured entry.

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